Cazuri clinice

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Intrahepatic cholangiocarcinoma – a rare indication for liver transplantation. Case report and review of the literature

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Rezumat

Colangiocarcinomul intrahepatic – o indicație rară de transplant hepatic. Prezentare de caz și recenzie a literaturii

Introducere: În timp ce carcinomul hepatocelular reprezintă o indicație unanim acceptată de transplant hepatic, colangiocarcinomul intrahepatic este o indicație controversată pentru transplant de ficat, datorită ratelor scăzute ale supraviețuirii globale și fără recidivă neoplazică posttransplant, înregistrate la acești pacienți. Totuși, în ultimii ani, unele centre au raportat rate satisfăcătoare ale supraviețuirii după transplantul hepatic efectuat pentru colangiocarcinoame, la pacienți selectați. În acest articol prezentăm caracteristicile clinico-patologice, conduita pre- și posttransplant, precum și rezultatele favorabile înregistrate în cazul unui pacient transplantat hepatic pentru un colangiocarcinom periferic nerezecabil. Considerăm că prezentarea unor astfel de cazuri cu evoluție favorabilă este utilă, întrucât colectarea datelor provenite din diverse centre poate contribui la identificarea unui grup de pacienți cu colangiocarcinoame, care pot beneficia de transplant hepatic.

Prezentare de caz: O pacientă de 62 de ani, cu ciroza de etiologie virală (VHB) și tumoră hepatică, a fost internată în centrul nostru pentru stabilirea conduitei terapeutice. Întrucât explorările imagistice și de laborator au sugerat un hepatocarcinom nerezecabil (datorită locației și afecțiunii hepatice subiacente), s-a decis că singura opțiune terapeutică având viză curativă este transplantul hepatic. Examenul histo-patologic al ficatului explantat a relevat un colangiocarcinom intrahepatic stadiul I dezvoltat pe un ficat cirotic. Evoluția post-transplant a fost favorabilă, iar în prezent, la 15 luni postoperator, pacienta este în viață, fără semne de recidivă neoplazică.

Concluzii: Transplantul hepatic poate reprezenta o opțiune terapeutică adecvată la pacienți selectați cu colangiocarcinom intrahepatic. Pacienții cu colangiocarcinoame în stadii incipiente, nerezecabile datorită afecțiunii hepatice subiacente, se pare că reprezintă principalul grup care beneficiază de transplant hepatic. Studii ulterioare sunt necesare pentru a identifica factorii de prognostic favorabil, în scopul selectării celor mai adecvați candidați pentru transplant. Cele mai adecvate regimuri (radio)chimioterapice și de imunosupresie trebuie să fie identificate în viitor, pentru a ameliora ratele supraviețuirii acestor pacienți.

Cuvinte cheie: colangiocarcinom, transplant hepatic, ciroză hepatică, chimioterapie

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Abstract

Background: While hepatocellular carcinoma is a common indication for liver transplantation, intrahepatic cholangio-

carcinoma represents a controversial indication for this procedure, due to lower disease-free and overall survival rates achieved by liver transplantation in such patients. Hence, in the last years, few centers reported satisfactory survival rates after liver transplantation for cholangiocarcinoma, in highly selected groups of patients. Herein we present the clinico-pathological characteristics, the pre- and postoperative management and the favorable outcome of a patient undergoing liver transplantation for an unresectable intrahepatic cholangiocarcinoma. We consider that reporting the patients with such favorable outcomes is useful, since collecting the data presented by different centers may contribute to identification of a selected group of patients with cholangiocarcinoma who may benefit from liver transplantation.

Case report: A 62-year old female patient with a primary liver tumor developed on HBV liver cirrhosis, was admitted in our center for therapeutical management. Since preoperative work-up suggested that the tumor is an unresectable hepatocellular carcinoma (due to its location and underlying liver disease), we decided to perform liver transplantation. The pathological examination of the explanted liver revealed that the tumor was a stage I intrahepatic cholangiocarcinoma. The postoperative course was uneventful, and in present, 15 months after transplantation, the patient is alive, without recurrence.

Conclusions: Liver transplantation may represent a valid therapeutical option in selected patients with intrahepatic cholangiocarcinoma. Patients with early stage intrahepatic cholangiocarcinomas unresectable due to the underlying liver cirrhosis seem to benefit mostly by liver transplantation. Further studies are needed to identify the favorable prognostic factors in order to select the most appropriate candidates for liver transplantation. The most suitable immunosuppressive and (radio)chemotherapic regimens should be identified in the future, in order to improve the disease-free and overall survival rates of the patients undergoing liver transplantation for intrahepatic cholangiocarcinoma.

Key words: cholangiocarcinoma, liver transplantation, liver cirrhosis, chemotherapy

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a malignant tumor developed from the intrahepatic bile ducts. It represents the second most common type of malignant primary tumor of the liver, after hepatocellular carcinoma (HCC) (1), and its incidence increases steadily over the last three decades all over the world (2-4).

The potentially curative treatment of ICC is liver resection, achieving 5-year overall survival rates up to 30% and median survival rates up to 27 months (5). Unfortunately, more than 50% of patients present with initially unresectable ICCs (6). In such instance, the median survival, achieved by palliative therapy, ranges between 2 and 11 months (7-9). The causes of unresectability may be represented by distant metastases, multiple bilobar lesions or centrally located lesion in patients with underlying liver disease such as viral/alcoholic chronic liver disease or liver cirrhosis. In the latter situation, the liver resection is precluded by the high risk of postoperative liver failure and not due to the extensive spread of the ICC. In such patients, liver transplantation has been proposed by several authors, as long as this approach allows complete removal of the primary tumor and it is also addressed to the underlying liver disease (10,11). The 5-year survival rates achieved by liver transplantation were about 29%, similar to those achieved by liver resection, but obviously higher than those achieved by palliative therapy (10). Hence, these survival rates are lower than those achieved in patients undergoing liver transplantation for other indications. Thus, most centers became reluctant to perform liver transplantation in patients with ICC. However, in the last decade, due to the very good results achieved, in selected patients with both intrahepatic and extrahepatic cholangiocarcinoma, by an aggressive approach consisting in radio-chemotherapy and liver transplantation (12), several authors reemphasized the role of liver transplantation in the management of cholangiocarcinoma (13,14).

In this article we report the case of a patient with centrally-located liver tumor and Child A HBV liver cirrhosis, undergoing liver transplantation. Preoperatively, the tumor was considered to be a HCC, but the pathological examination of the tumor revealed an ICC. Since ICC is considered a controversial indication for liver transplantation due to the higher rates of recurrence and lower 5-year survival rates, we decided to present this case-report due to the favorable outcome of this patient. Thus, we believe that our experience may contribute, by corroboration with similar good results reported by other centers, to identify, in the future, a selected group of patients with ICC who may really benefit by liver transplantation. In this case-report we present the clinic-pathological characteristics, the management and the outcome of our patient and perform a review of the literature on this topic.

Case report

A 62-year old female patient, with medical history of hypothyroidia (since 2000, under treatment with Levothyroxinum 50 mg daily), high blood pressure (since 2005, under treatment with Metoprololum 50 mg daily), lumbar disc hernia operated in 2005, and HBV infection diagnosed in June 2010 (HBs Ag positive, HBe Ab positive and HBc Ab IgG positive), was diagnosed, during follow-up for chronic liver disease, with an 8-cm liver tumor. The patient was admitted in our center on December 6th 2010 for evaluation and therapeutical management.

Upon admission, physical examination revealed an obese patient (84 kg weight, 1.65 m height, BMI = 30.85 kg/m^2), with mild sclera jaundice, without fever, with normal consciousness status. Abdominal examination showed absence of abdominal distension or ascites and the presence of the inferior border of

the liver 1 cm below right costal margin.

Laboratory findings revealed: WBC 8240/mm3, HGB 14.8 g/dl, PLT 260000/mm^3, AST 159 U/l, ALT 73 U/l, AlkP 688 U/l, GGT 1543 U/l, Bil T 2.93 mg/dl, Urea 24 mg/dl, Creat 0.65 mg/dl, Chol 246 mg/dl, Na 141 mmol/l, K 4.6 mmol/l, Cl 105 mmol/l, INR 1.03, PT 12 sec, AFP 2.37 ng/ml, CA 19-9 41.70 U/ml, CEA 0.81 ng/ml.

Abdominal ultrasound examination revealed an 8-cm tumor of the liver, centrally located, without evidence of ascites or splenomegaly. Contrast-enhanced abdominal CT scan pointed out a 9/7 cm liver tumor involving segments 3, 4, 5, and 8, presenting arterial phase flash and late phase wash-out, with non-homogenous structure. The tumor was adjacent to the intrahepatic right portal branch, but there is no evidence of macrovascular invasion or portal vein thrombosis. The caudal part of the tumor was in the close proximity of the vasculobiliary structures of the hepatic hilum and a mild dilation of the intrahepatic bile ducts has been noted. Taking into account the radiological features of the tumor, the radiologists concluded that the tumor is a hepatocellular carcinoma (Fig.1).

Thoracic CT scan and bone scintigraphy revealed no evidence of lung or bone metastases.

Upper gastro-intestinal endoscopy revealed portal hypertension-induced gastropathy and total colonoscopy was normal.

Taking into account all these findings, the diagnosis was liver tumor (probably hepatocellular carcinoma) developed on Child A HBV liver cirrhosis (MELD 7). The curative therapeutic options were liver resection or liver transplantation. Due to the size and location of the tumor, in order to achieve its complete resection, the patient should undergo a left trisectionectomy. Hence, because of the underlying liver disease, the risk of postoperative liver failure would be unacceptable high. Thus, the only curative therapeutic option in this patient was liver transplantation.

After completing pre-transplant work-up (mammography, gynecologic, cardiologic, and psychological evaluation), the patient was listed for liver transplantation.

On December 16th 2010, an isogroup liver graft from a brain-dead donor was available and the patient underwent liver transplantation.

Pathological examination of the explanted liver revealed an 8-cm intrahepatic cholangiocarcinoma, without vascular invasion (pT1). The lymph nodes did not present metastases (N0). Non-tumoral liver parenchyma presented liver cirrhosis. Thus, the postoperative staging revealed a stage I (T1N0M0) intrahepatic cholangiocarcinoma (according to AJCC staging system – 6th edition) - (Fig. 2).

For induction of immunosuppression we used Baziliximab and Methylprednisolone, delivered intraoperatively. Postoperatively, the patient received the second dose of Baziliximab by the fourth postoperative day. For the immunosuppression maintenance we used initially Sirolimus and Cell-cept.

Postoperative course was uneventful, the patient being discharged in the 20th postoperative day, in good clinical condition and presenting normal values of the liver function tests.

The patient started adjuvant chemotherapy by the 27th day after transplantation. The chemotherapeutic regimen consisted in 6 cycles of Gemcitabine and Oxaliplatin (January 2011 – May 2011).

Cell-cept was withdrawn three months after liver transplantation. Thus, in present, Sirolimus is the only immunosuppressant agent used.

To avoid HBV recurrence, the patient receives Hepatitis B Immunoglobulin (2000 IU when the plasma level of HBs Ab is less than 200 IU/l) and Lamivudine 100 mg daily.

The follow-up consists in abdominal ultrasonography, hemoleucogram, liver function tests and sirolinemia assessment monthly in the first year post-transplant, and every three months afterward, dosage of the CA 19-9, CEA and

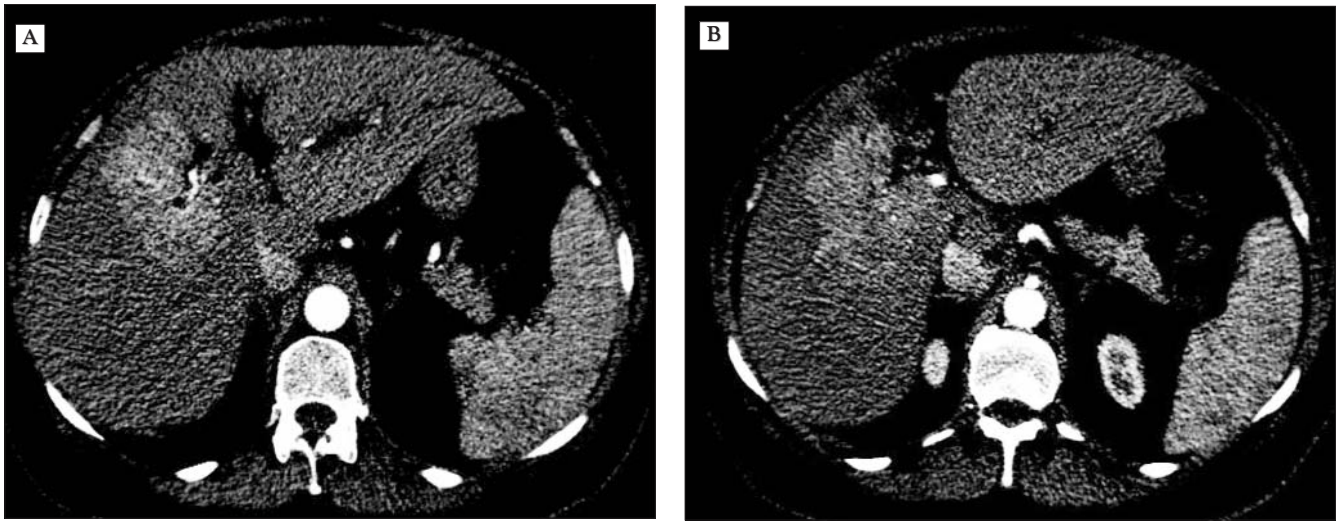

Figure 1 (A,B). *Contrast-enhanced abdominal CT scan- 8/7 cm liver tumor involving segments 3, 4, 5, and 8, presenting arterial phase flash and late phase wash-out, with non-homogenous structure*

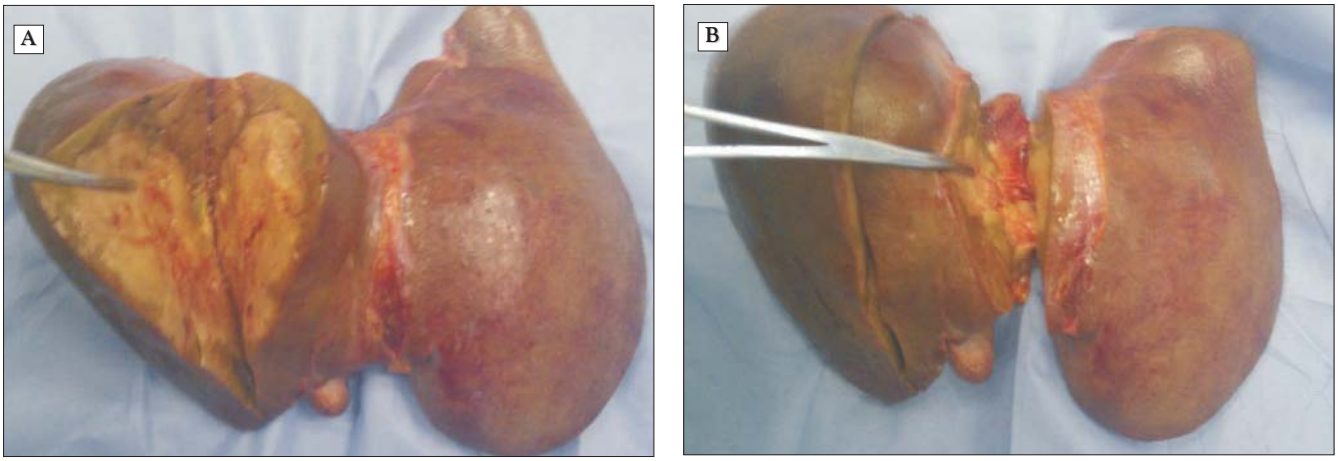

Figure 2. *Macroscopic view of the specimen- total hepatectomy of the cirrhotic liver with a 8/7 cm tumor located in segments 3, 4, 5 and 8*

AFP every three months and thoracic CT scan and abdominal MRI/CT scan every 6 months.

In present (15 months after liver transplantation), the patient is disease-free, without evidence of recurrence on imaging exams, and normal laboratory tests: WBC 6520/mm^3, HGB 13.5 g/dl, PLT 292000/mm^3, AST 26 U/l, ALT 47 U/l, AlkP 175 U/l, GGT 39 U/l, Bil T 0.37 mg/dl, Urea 19 mg/dl, Creat 0.7 mg/dl, Chol 211 mg/dl, Na 143 mmol/l, K 4.3 mmol/l, Cl 102 mmol/l, INR 0.95, AFP 2.04 ng/ml, CA 19-9 7.58 U/ml, CEA 0.74 ng/ml, Sirolinemia 5.48 ng/ml.

Discussion

Traditionally it was considered that the development of ICC is not related to chronic viral hepatitis or cirrhosis. Hence, in the last two decades, several reports identified an association between HBV or HCV infection and ICC (15-17) and an increased risk for developing ICC in patients with liver cirrhosis, regardless its etiology (18). This possible association between chronic liver disease and ICC should be take into account in patients with liver tumors developed on liver cirrhosis, especially when liver transplantation is considered.

In our patient, the radiological features of the liver tumor suggested a HCC. In present, because the specificity of contrast-enhanced CT scan in diagnosis of HCC is about 93% (19), most centers do not recommend the routine use of biopsy for the liver tumors greater than 2 cm diameter and typical CT-scan features of HCC, in cirrhotic patients (20-22). Hence, the only way to avoid the miss-diagnosis of a liver tumor in a cirrhotic patient seems to be the routinely performance of the biopsy. This is of peculiar importance in cirrhotic patients with liver tumors listed for liver transplantation, since liver transplantation is widely accepted as treatment of choice for HCCs on cirrhosis, while ICC is a controversial indication for liver transplantation. Thus, the data collected in the European Liver Transplant Registry revealed that, between 1988 and 2008, liver transplantation for ICC was performed in 294 patients out of 10199 patients undergoing liver transplantation for malignant disease (2.9%) (23).

The treatment of choice in patients with ICC is liver resection, achieving 5-year overall survival rates about 30% in patients treated with curative intent. Hence, most patients with ICC are not suitable for liver resection at the time of diagnosis, either due to the extrahepatic spread of the disease, or because the insufficient volume of the remnant functional liver parenchyma after hepatectomy (6). The later situation is usually met in patients with ICC developed on chronic liver disease (mainly liver cirrhosis). In these patients, palliative treatment is usually employed, with overall survival rates ranging between 2 and 11 months (7-9).

The patient presented above, should require a left trisectionectomy in order to remove the liver tumor, but due to the HBV liver cirrhosis, the risk of postoperative liver failure was unacceptable high, so liver resection was precluded. In this instance, the only potentially curative treatment was represented by liver transplantation. We recommended this approach due to the supposition that the liver tumor is a HCC, based on the radiological features of the tumor. Although pathological evaluation revealed an ICC, we consider that the patient underwent the only potentially curative treatment in her situation, since liver resection was ruled out due to the risk of postoperative liver failure. Thus, liver transplantation was the only treatment giving the chance of a long-term survival to this patient, since any other treatment would bring a life expectancy less than one year to such patients.

Although initially the patients with ICC were considered good candidates for liver transplantation, the 3-year disease-free survival rates less than 35% and the 5-year survival rates less than 20% achieved by this treatment, were considered disappointing (11,24-26). Due to the high tumor-recurrence rates, lower survival rates and donor organ shortage, allocation of a liver graft to a patient with a 5-year life expectancy less

than 50% was considered questionable (27,28). Due to these reasons, most centers became reluctant to accept ICC as an indication for liver transplantation (24,26,29).

Hence, in the last decade, a better selection of patients, based on clinico-pathological prognostic factors and response to neoadjuvant radio-chemotherapy, allowed achieving better results in patients undergoing liver transplantation for cholangiocarcinomas (14,25,30). On the other hand, the developing of living donation and the extensive use of marginal grafts from brain-dead donors raises new questions about the acceptance of patients with ICCs for transplantation (10). Corroborating these aspects, several centers tried to identify those favorable prognostic factors correlated with a good post-transplant outcome, in order to define a selected group of patients with ICC, which may benefit for liver transplantation.

Thus, in a recent study, published in 2011, Hu et al. revealed, by multivariate analysis, that the independent prognostic factors for a poor overall survival were multiple tumors, lymph nodes metastases and macrovascular invasion, while the independent risk factors predicting a poor disease-free survival were multiple tumors and lymph nodes involvement (11). Another retrospective study published in 2011, comparing the results achieved by liver transplantation and liver resection for both ICC and ECC, revealed that multivariate factors predictive for worse survival outcome included hilar cholangiocarcinoma, multifocal tumors, perineural invasion and liver resection as the treatment modality compared with liver transplantation (14). Earlier reports identified as negative prognostic factors the tumor size greater than 5 cm, the recurrence of ICC (after liver resection) before liver transplantation, presence of distant metastases, direct invasion of the adjacent organs, positive surgical margins and advanced pTNM staging (31-34). The good outcome of our patient may be attributable to the favorable clinico-pathological prognostic factors: single lesion, without lymph nodes metastases, no vascular or adjacent organs invasion, absence of extrahepatic metastases, negative surgical margins and early TNM stage. The only potentially pejorative prognostic factor in our patient was tumor size, although Hong et al. revealed in a recent study that tumor size larger than 5 cm was not predictor of poor outcome in patients with ICC undergoing liver transplantation (14).

However, even in patients with good clinico-pathological prognostic factors, the 5-year overall survival rates in patients with cholangiocarcinomas undergoing OLT without adjuvant therapy did not exceeded 20% in most series, the cause of death being the malignant disease relapse (14,24-26). Thus, it is obviously necessary to use an effective adjuvant therapy in such patients, in order to increase survival rates. Although there are no randomized controlled trials revealing the benefit of adjuvant therapy in patients with ICC, the results reported by two recent retrospective studies, in highly selected groups of patients with both ICC and ECC undergoing liver transplantation and radio-chemotherapy, highlighted the importance of radiotherapy and chemotherapy in such patients (14,35). Thus, in patients undergoing liver transplantation and no chemo-radiation therapy the 5-year survival rate was 20%, statistically significant lower than those achieved in patients receiving adjuvant therapy (33%) or neoadjuvant and adjuvant chemo-radiation (47%) (14). Moreover, in patients with ICC and poor prognostic factors treated by curative resection, the use of an adjuvant Gemcitabine-based chemotherapy regimen enables significantly higher 3-year survival rates than in similar patients undergoing liver resection without any adjuvant therapy (59.6% vs. 18.9%, p value < 0.01) (36).

Since in our patient the diagnosis of ICC was revealed by pathological examination of the explanted liver, we did not deliver preoperative chemotherapy, but we started, as soon as possible after transplantation, the adjuvant chemotherapy. The disease-free status of our patient at 15 months after liver transplantation may be (at least) partially attributable to the adjuvant chemotherapy regimen.

Anyway, this outcome is obviously superior to those achieved by palliative therapy.

In an attempt to avoid the potentially carcinogenic effects of the calcineurin inhibitors, we decided to use a Sirolimus-based regimen for immunosuppression maintenance, taking into account its antiproliferative properties (37).

Conclusions

Liver transplantation may represent a valid therapeutical option in selected patients with intrahepatic cholangiocarcinoma. Patients with early stage intrahepatic cholangiocarcinomas unresectable due to the underlying liver cirrhosis seem to benefit mostly by liver transplantation. Further studies are needed to identify the favorable prognostic factors in order to select the most appropriate candidates for liver transplantation. The most suitable immunosuppressive and (radio)chemotherapic regimens should be identified in the future, in order to improve the disease-free and overall survival rates of the patients undergoing liver transplantation for intrahepatic cholangiocarcinoma.

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